Drug-induced parkinsonism

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Learning objectives

At the conclusion of this educational program, learners will be able to:

- 1) Discuss common risk factors, causative agents and clinical presentations in DIP
- 2) Discuss treatment and clinical outcomes in DIP
- 3) Discuss the potential relationship of DIP to PD

Drug-induced parkinsonism (DIP)

- Culprit drugs and mechanisms of DIP
- Epidemiology (Incidence, prevalence, risk factors)
- Clinical presentation
- Treatment and outcomes
- (When) Does DIP reveal underlying neurodegenerative disease?

Culprit drugs and mechanisms in DIP

Agents associated with DIP

- French pharmacovigilance center reporting 1993-2009

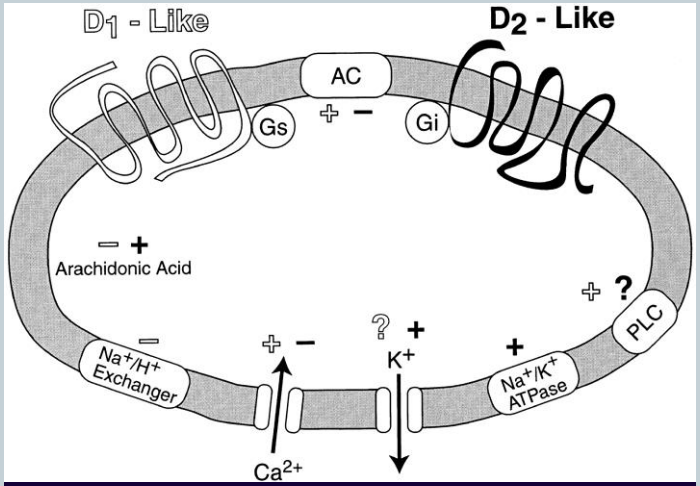
Class	Agents	% of reports
Central dopaminergic antagonists	haloperidol, fluphenazine, chlorpromazine, risperidone, olanzapine	49
Anti-depressants	citalopram, paroxetine, venlafaxine	8
Calcium channel blockers (T)	flunarizine, cinnarizine, verapamil, diltiazem	5
Peripheral dopaminergic antagonists	metoclopramide, domperidone	5
H1 anti-histamines	alimemazine, hydroxyzine	5
Miscellaneous	valproate, lithium, amiodarone (not all drugs were detailed)	28

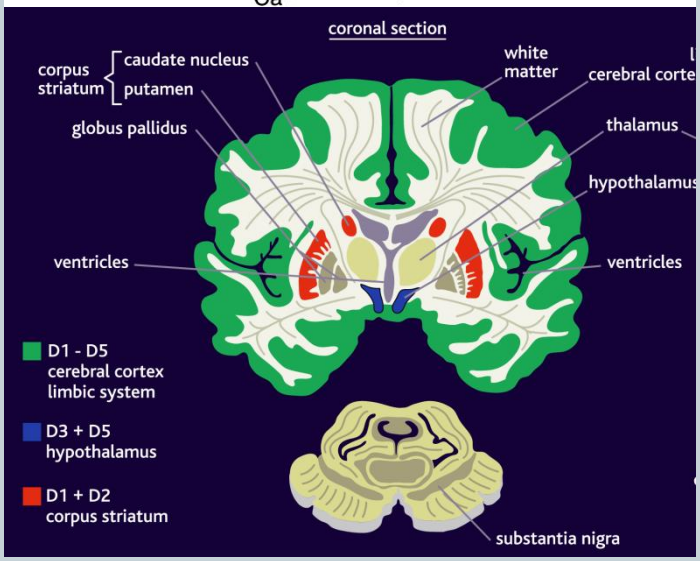
- **Dopamine antagonism is a common theme**

Bondon-Guitton *Mov Disorders* 2011

Dopamine receptor pharmacology

- Three major DA systems
  - Nigrostriatal, mesolimbic/mesocortical, tuberoinfindibular
- 5 DA receptor subtypes
  - D1-like (D1/D5) and D2-like (D2/D3/D4)
- Differ in coupling and distribution

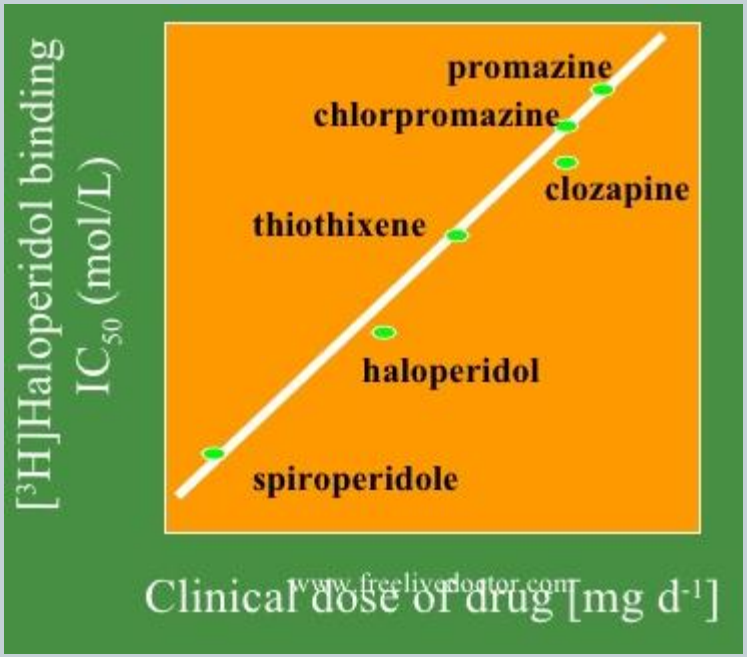




Rang *Pharmacology* 2001; Missale *Physiol Rev* 1998

APs act through multiple transmitter pathways

- AP motor and behavioral effects through DA and extra-DA
- AP potency defined by relative D2 affinity
- Cholinergic, serotonergic, adrenergic tone affects DA mediated motor pathways



Spectrum of AP AEs mediated by diverse receptors

TABLE

RECEPTOR BLOCKADE AND ANTIPSYCHOTIC SIDE EFFECTS[2]

Receptor Type	*Side Effects*
D_2	EPS, prolactin elevation
M_1	Cognitive deficits, dry mouth, constipation, increased heart rate, urinary retention, blurred vision
H_1	Sedation, weight gain, dizziness
α_1	Hypotension
5-HT_{2A}	Anti-EPS (?)
5-HT_{2C}	Satiety blockade

D=dopamine; EPS=extrapyramidal symptoms; M=muscarine; H=histamine; 5-HT=serotonin.

Robinson DS. *Prim Psychiatry*. 2007

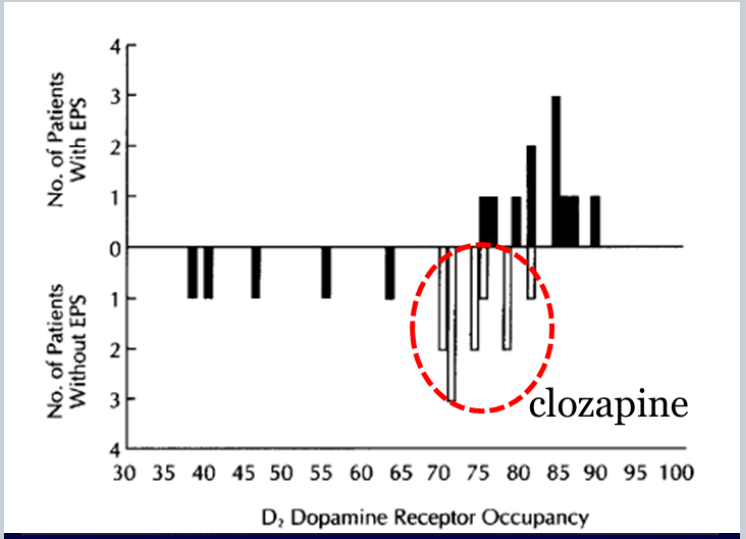
Receptor pharmacology of AP drugs

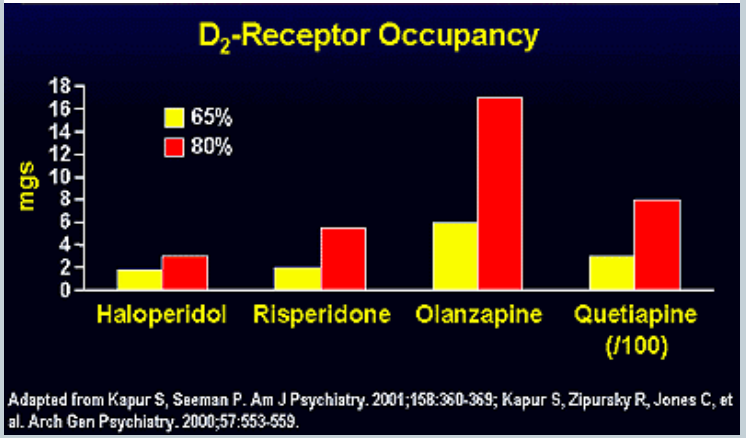
Drug	D2	5HT2A	α1	H1	M1
First generation or "typical" APs					
haloperidol	1.5	53	12	>1000	>>1000
perphenazine	0.75	5.6	10	8	>1000
Second generation or "atypical" APs					
aripiprazole	0.5	3.4	47	61	>1000
risperidone	4	0.5	0.7	20	>1000
ziprasidone	5	0.4	11	50	>1000
olanzapine	11	4	19	7	1.9
clozapine	126	16	7	6	1
quetiapine	770	31	8	19	>1000

Values are Ki (nM)—Low values represent high affinity

DIP is related to D2 occupancy

- D2 Receptor occupancy drives DIP
- Occupancy threshold approximates extent of nigral degeneration at onset of PD
- Drugs with different potencies cause DIP at similar D2 occupancy





Farde et al. *Arch Gen Psych* 1992

Culprit drugs and mechanisms in DIP

Many drugs implicated but APs most common

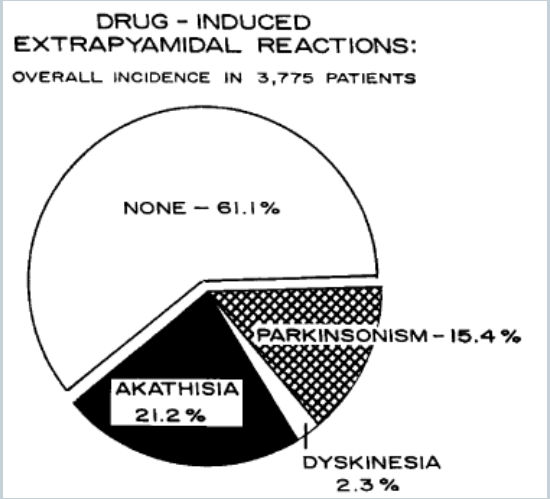
Dopamine antagonism (D2R occupancy) is a common thread

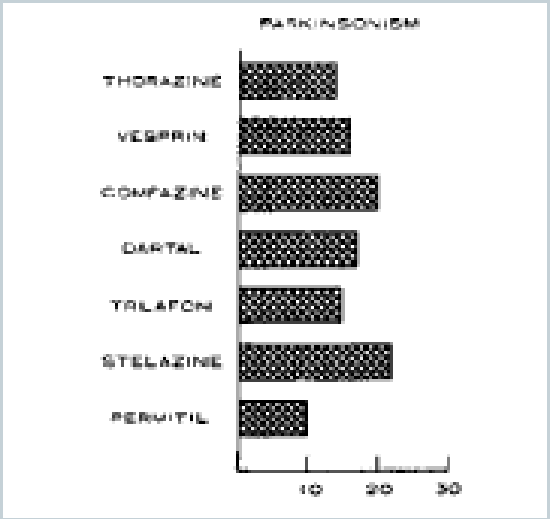
Modulation by 5HT and other pathways

Epidemiology and determinants of DIP

Epidemiology of DIP

- Ayd (1961) described EPS in >3000 AP-treated pts
- Parkinsonism in ~15%
- Estimates vary from study to study (~10-60%)
- 10-20% estimated in common practice
- Associated with non-compliance, falls, decreased QOL (Schouten et al *JAMDA* 2012)

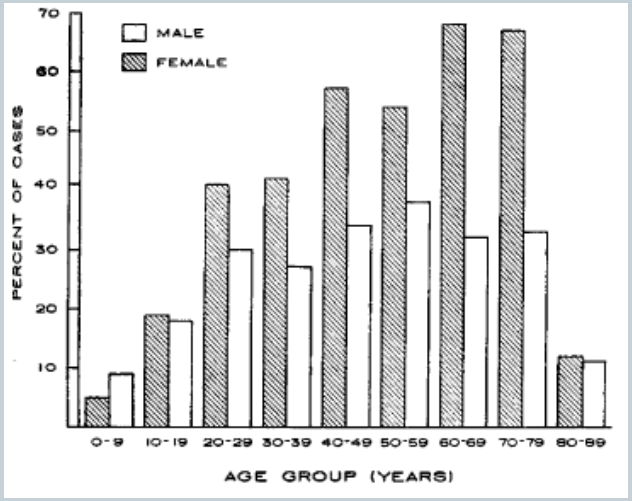


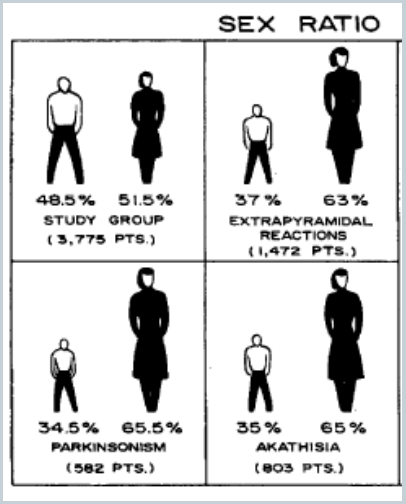


Ayd *JAMA* 1961

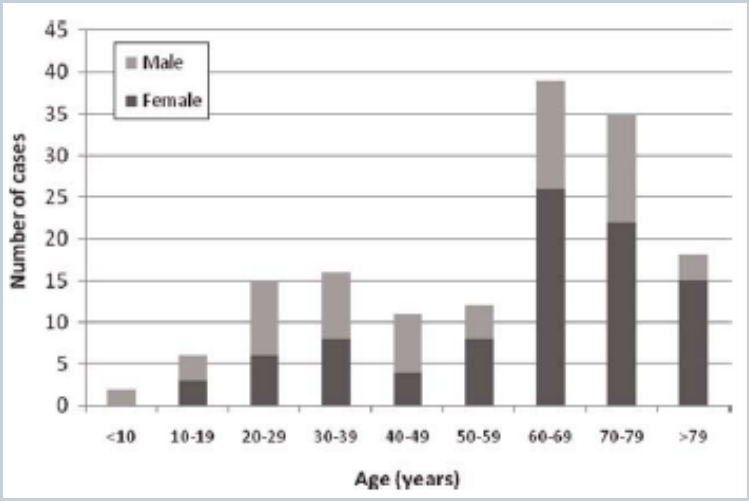
Risk factors for DIP

- Increasing age and female gender





Ayd (1961)



Bondon-Guitton (2011)

- Intensity (dose, duration) also well-described

Risk factors for DIP

- Intensity (dose, duration) also well-described
- HIV
- Personal> family history of EPS
- DA receptor polymorphisms, ?other genes
- Cigarette smoking may be protective (as in PD)

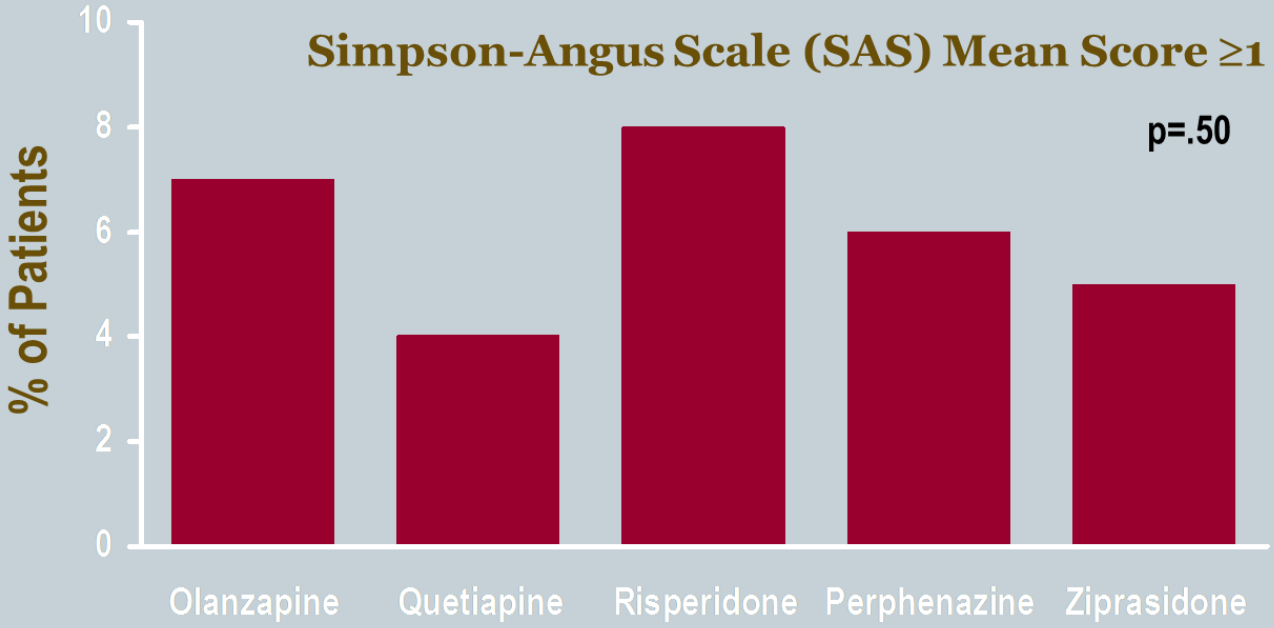
DIP: Second-Generation Antipsychotics

- RIS* (2-16 mg)=11.8% vs. HAL (20 mg)=26.4% vs. PBO=3.4%
- OLZ (13 mg)=14.1% vs. HAL (12 mg)=37.9%
- QTP (75-750mg)=4-8% vs. HAL (12 mg)=29% vs. PBO=10%
- ZIP (110 mg)=9% vs. HAL (9 mg) = 22%
- ARI (2-30mg)=6% vs. HAL (5-20mg) =19.5%

Simpson GM, Lindenmayer JP. *J Clin Psychopharmacol*. 1997;17(3):194-201. Tollefson GD, et al. *Am J Psychiatry*. 1997;154(4):457-465. Arvanitis LA, Miller BG. *Biol Psychiatry*. 1997;42(4):233-246. Hirsch SR, et al. *J Clin Psychiatry*. 2002;63(6):516-523. Marder et al 2003. Weiden et al 2008. Kane et al 2010.

DIP with SGAs in a large randomized trial

CATIE trial: >1800 pts in RCT of different APs for schizophrenia



**Secondary analysis with more inclusive criteria (Miller *BMJ* 2008) increased incidence to 20-30% but no difference between drugs

Lieberman JA, et al. *N Engl J Med*. 2005

DIP is a common cause of Parkinsonism

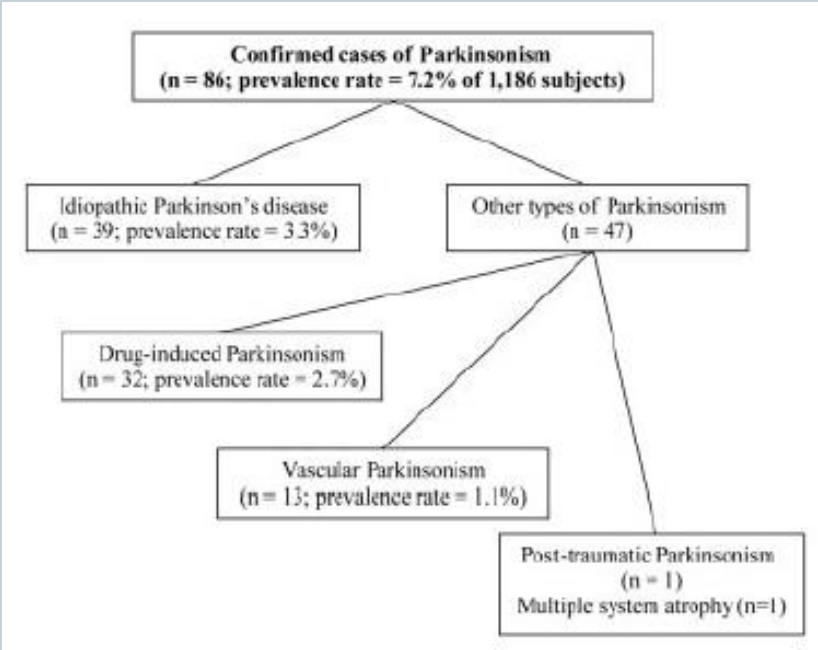
- 2nd most common after PD
- Expanding problem

  -AP rx's increasing for a variety of indications

  -~60% off-label in VA

  (Leslie 2009)

--Common (and challenging!) differential



Barbosa et al. *Mov Disord* 2006

DIP is likely underdiagnosed

- 48 psychiatric inpatients
- Compared clinical diagnoses of DIP and other EPS to clinical diagnoses

TABLE 1. Research and Clinical Diagnoses of Neuroleptic-Induced Extrapyramidal Syndromes in 48 Psychotic Patients

Extrapyramidal Syndrome	Patients Given Research Diagnosis	Clinical Diagnosis: Patients Given Diagnosis	Clinical Diagnosis: Percent of Patients Given Research Diagnosis	McNemar Test of Difference Between Clinician and Researcher Errors: χ^2 (df=1)	p
Dystonia	3	1	33	—	—
Parkinsonism	29	17	59	10.08	<.005
Akinesia	23	14	61	7.11	<.01
Akathisia	27	7	26	18.05	<.001
Tardive dyskinesia[a]	10	1	10	7.11	<.01

- Only 59% of DIP clinically diagnosed
- Similar results in a study of inpatient neurologic consultations (Friedman et al. *J Gerontol* 2003) where only 45% identified correctly

Weiden *Am J Psych* 1987

Epidemiology and determinants of DIP

DIP is common and disabling

Seen with both FGAs and SGAs

RFs include age, gender

Variability suggests unmeasured individual susceptibility

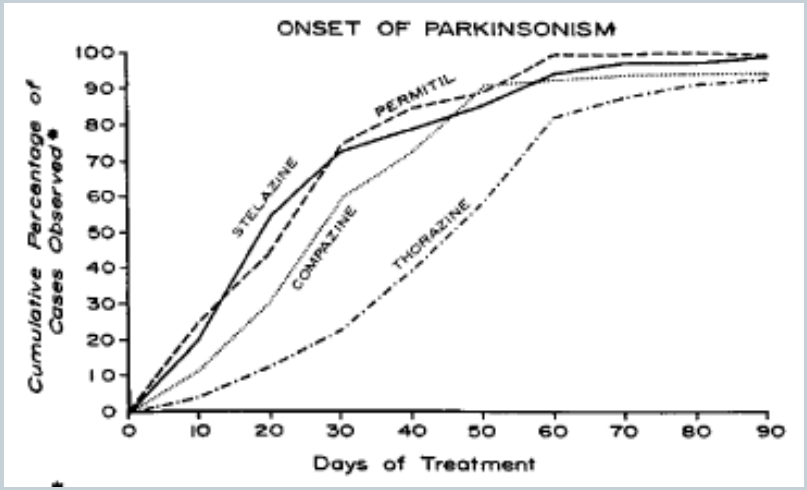
Magnitude of the problem is under-recognized

Likely to increase

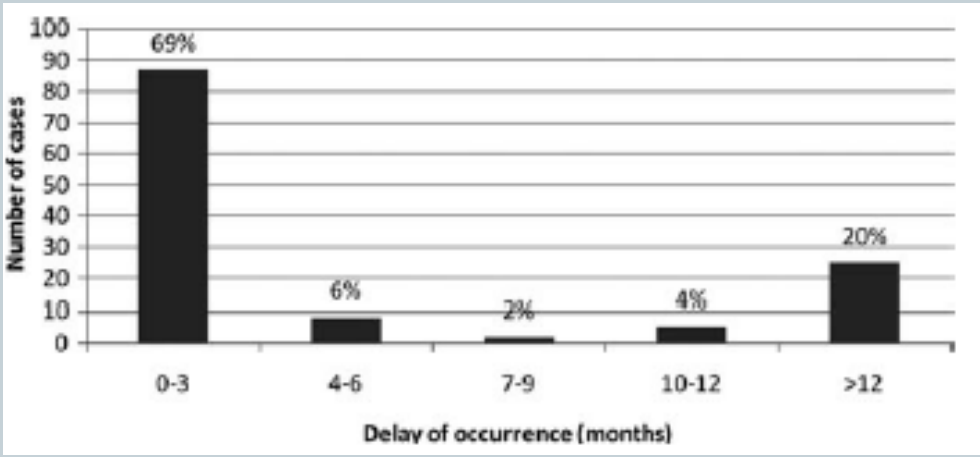
Clinical Characteristics of DIP

Timing of drugs and DIP

Ayd (1961)



Bondon-Guitton (2011)



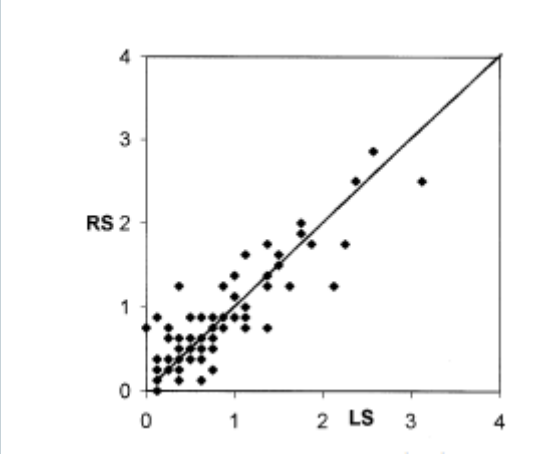
DIP is commonly but not always observed soon after a drug is started

Clinical characteristics of DIP

Giladi group (Israel). 75 pts (72% male). Mean age 43. Most chronically (>10y) treated

Table 1. The motor performance as scored in subscales of the UPDRS and the ADL score of the UPDRS in 75 patients with NIP

Subscales[8]	Maximum obtainable score	Mean ± SD	Range
Total motor score	108	22.6 ± 14.3	3, 72
Global tremor score	24	3.0 ± 4.3	0, 18
Global bradykinesia score	36	9.8 ± 6.1	1, 28
Global rigidity score	20	5.6 ± 4.1	1, 18
Upper body score	12	2.7 ± 1.9	0, 9
Lower body score	12	2.1 ± 1.8	0, 8
Gait score	8	1.0 ± 1.4	0, 8
Postural impairment gait difficulty	20	1.9 ± 2.8	0, 20
Right score	32	7.0 ± 4.7	1, 23
Left score	32	6.9 ± 5.1	0, 25



Relatively little tremor, symmetric signs otherwise not very different than PD

Hassin-Baer *J. Neural Trans.* 2001

Asymmetry of findings in DIP

- Sethi and Zamrini *J Neuropsych and Clin Neuro 1990*
- 20 pts: 5 women, mean age 59
- Metoclopramide in 5 pts (tx 3-9mos), APs in 15 (3-25 years)
- Predominant signs:
  - Tremor in 7
  - Bradykinesia in 5
  - Mixed for 8
- Significant asymmetry in 6 (30%)

- Hardie and Lees (*JNNP* 1998) described asymmetry in 14/26 schizophrenic patients with DIP (54%)

Treatment of DIP

- Does it need to be treated?
- Removal, reduction or substitution
- Little systematic study
  - One crossover placebo controlled trial (40 pts, 2wk treatment)

    amantadine=trihexyphenidyl>placebo

  Empiric use of anti-cholinergics but AEs often limiting
- Variable response to levodopa
  - May be safer than advertised
- Several reports of ECT in severe cases

Response to levodopa in DIP

	Webster score		Duration (months) of levodopa			
Patient	*Pre/post*	*Response*	*Delay*	*Treatment*	*Follow up*	*Dose mg*
Drug withdrawn						
CR	12/10	none	0	29	30	1000*
KS	15/16	none	0	3	3	600
AK	10/6	slight	1	7	15	300*
AN	22/17	slight	4	30	30	600
ES	26/18	slight	3	9	10	600
AD	11/4	moderate	0	2	30	1000*
JK	14/8	moderate	0	21	21	300
AS	11/3	moderate	2	39	39	150
JS	23/0	complete	1	24	24	300
PW	13/2	complete†	1	6	23	300
Drug continued						
NW	10/11	none	—	12	28	800*
MC	15/15	none	—	6	12	800*
KG	20/15	slight	—	47	53	1000*
GT	23/14	moderate	—	33	33	800
ON	18/6	moderate	—	26	26	300

LD response	Drug withdrawn	Drug continued	Overall
None	20%	40%	27%
Slight	30%	20%	27%
Moderate	20%	40%	33%
Complete	20%	0%	13%

Discontinuation for “agitated anxiety” in 1 pt, dyskinesia in 2

Hardie and Lees *JNNP* 1998

Outcomes in DIP

- Typical thinking is withdraw and wait (but how long?)
  - Stephen and Williamson *(Lancet* 1984*)*:66% of 48 pts with complete resolution at 36 weeks (mean 7 weeks) but 11% with persistent sx at 18 months
  - 10/16 (62%) pts from Hardie and Lees had residual sx at 3-4 months that required levodopa
  - Lim et al. (*Int J Neurosci* 2013) reported 2 cases of persistent symptoms for more than 6 months with normal dopamine transporter imaging—eventually resolved after 9-12 months

Comparing DIP to PD

Main features	DIP	iPD
Age at onset	More often in the elderly	Sixth decade
Symptoms at onset	Typically symmetrical	Typically asymmetrical
Onset	Acute or subacute	Chronic
Course with treatment	Reversible	Progressive
Response to causative drug withdrawal	Variable	Poor
Response to levodopa	Poor	Marked
Other features	Orofacial dyskinesia, akathisia	
Rest tremor	Uncommon	Common
Sex	More common in females	More common in males
Freezing	Uncommon	Common

Lopez-Sendon *Drugs Aging*. 2012

Does DIP reveal underlying neurodegeneration ?

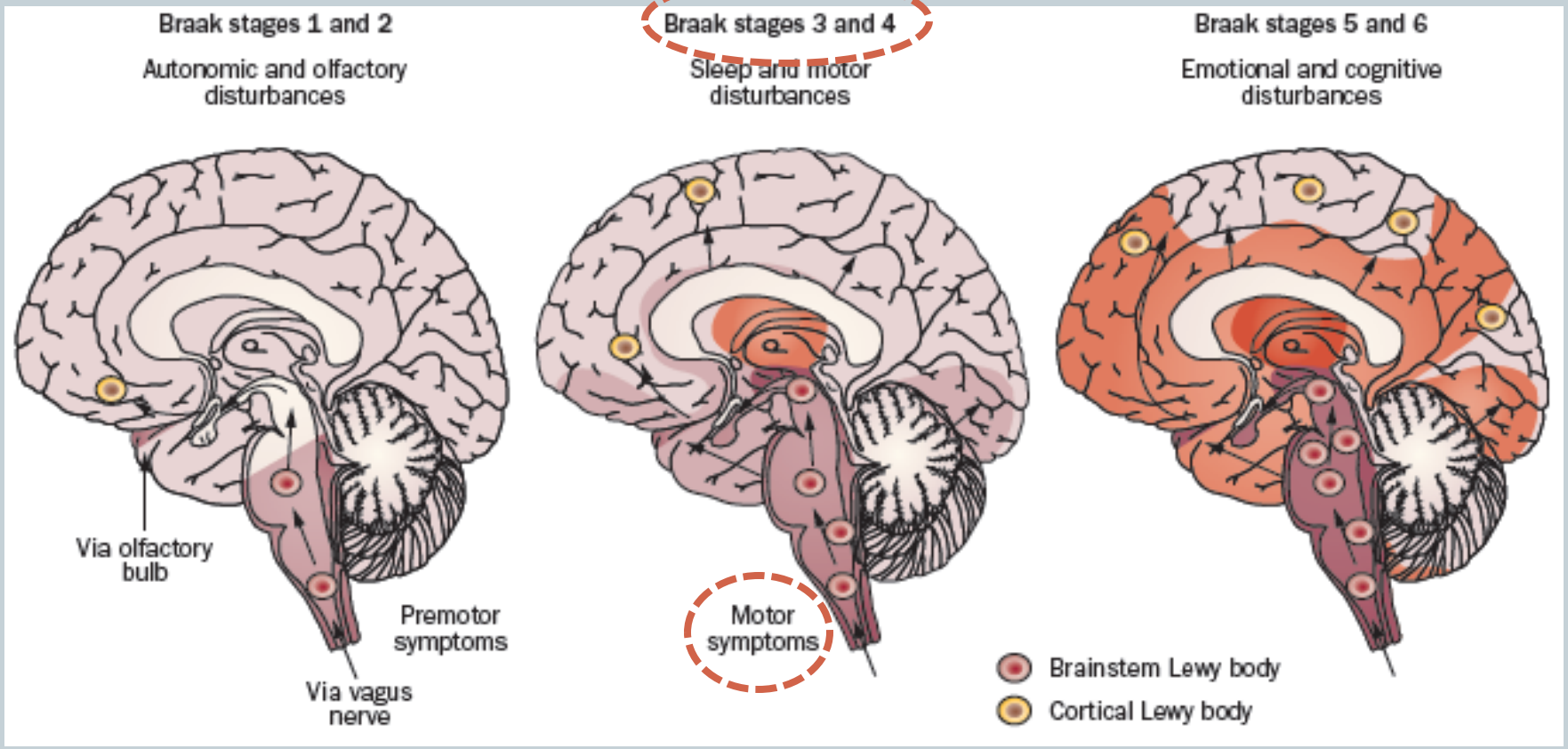
Evidence for "unmasking" of PD in DIP

- ~10-20% with persistence or worsening after withdrawal
- Multiple studies describe pts who resolve but develop recurrent, progressive sx
- Rajput et al. (*Arch Neurol* 1982) reported 2 pts reversible DIP but nigral Lewy bodies at autopsy
- Patients with prior DIP are at ~20X higher risk for PD

Some DIP patients have dopaminergic denervation

Study	N	Population	Method	Abnormal scans
Burn *Neurology* 1993	13	schizophrenia	F-dopa PET	4 (30%)
Lorberboym *Mov Dis* 2006	20	mixed	DaT-SPECT	11 (55%)
Tinazzi *Mov Dis* 2008	32	mixed	DaT-SPECT	14 (44%)

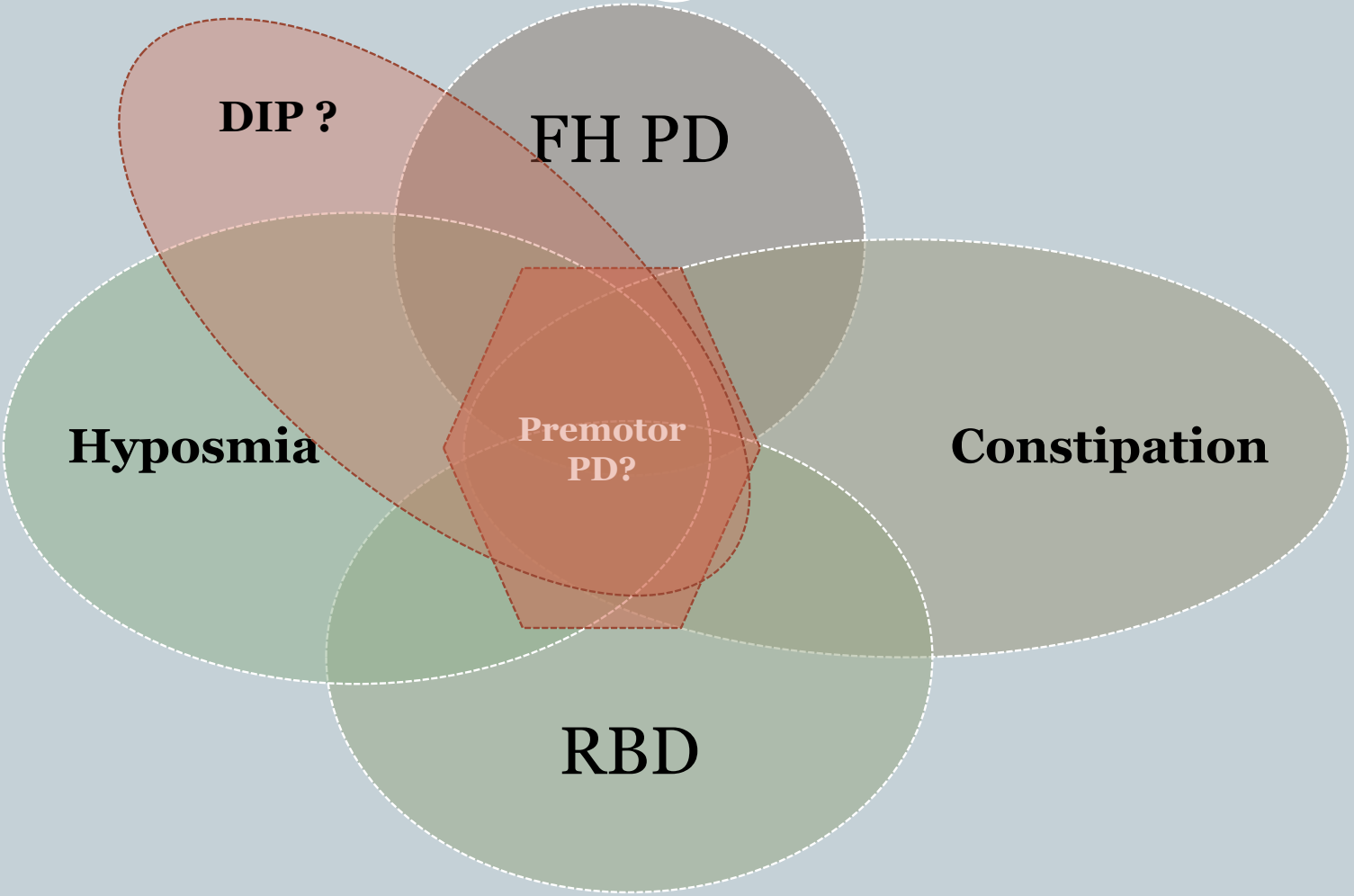
Progression of Lewy pathology in PD



Braak, Neurobiol Aging, 2003

Halliday, Mov Disord, 2011

Does DIP reveal underlying neurodegeneration?



Does DIP reveal underlying neurodegeneration?

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Motor and non-motor features of Parkinson's disease that predict persistent drug-induced Parkinsonism

James F. Morley [a,b,*], Stephanie M. Pawlowski [a], Adhithi Kesari [a], Ivy Maina [a], Alexander Pantelyat [a,b], John E. Duda [a,b]

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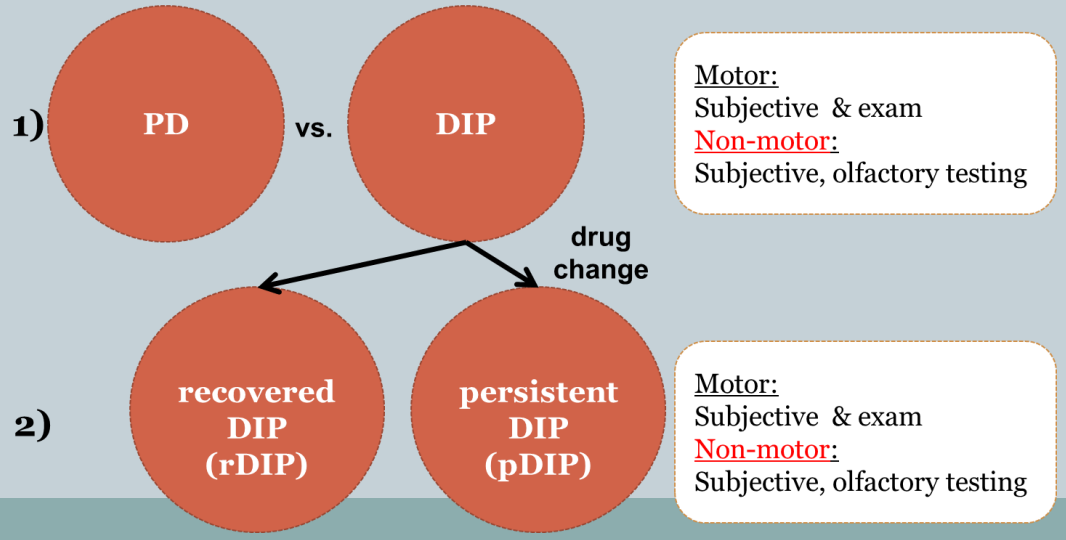
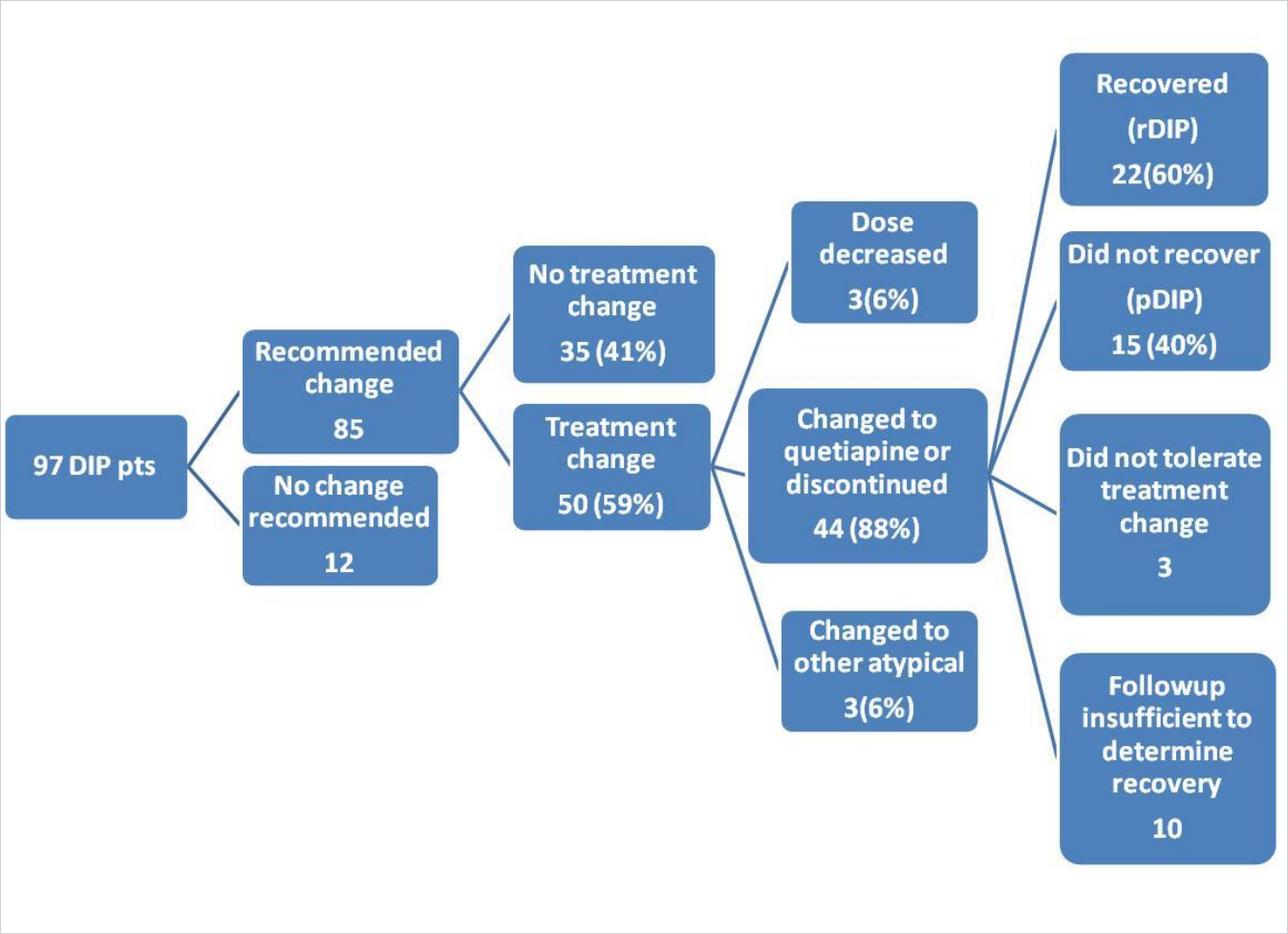


Clinical outcomes of DIP in the PADRECC cohort



A cohort to compare DIP with PD

	PD vs. DIP			Persistent DIP vs. reversible DIP		
	PD N=97	DIP N=97	P	pDIP N=15	rDIP N=22	p
Age	65 (6.8)	64 (10)	0.58	69 (11)	63 (10)	0.10
Gender (% male)	99	95	0.11	100	93	0.41
Smokers (%)	17	21	0.63	27	19	0.66
UPDRS-I	3.5 (2.9)	5.6 (3.7)	0.002	2.8 (2.5)	4.3 (4.3)	0.44
UPDRS-II	13 (8.9)	13 (8.5)	0.81	11 (10)	7.4 (6.3)	0.25
Schwab & England	76 (20)	70 (25)	0.13	70 (23)	80 (21)	0.27

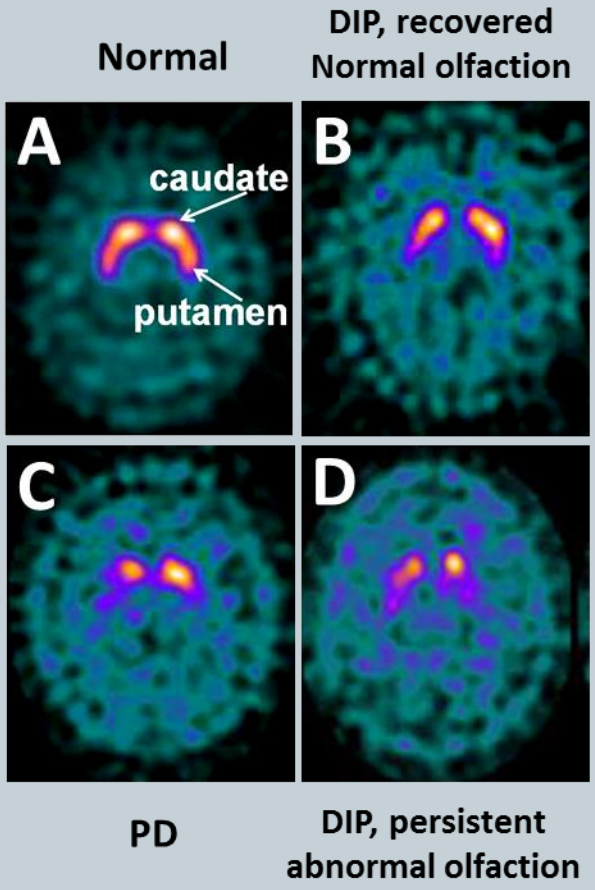
Motor features in PD and DIP

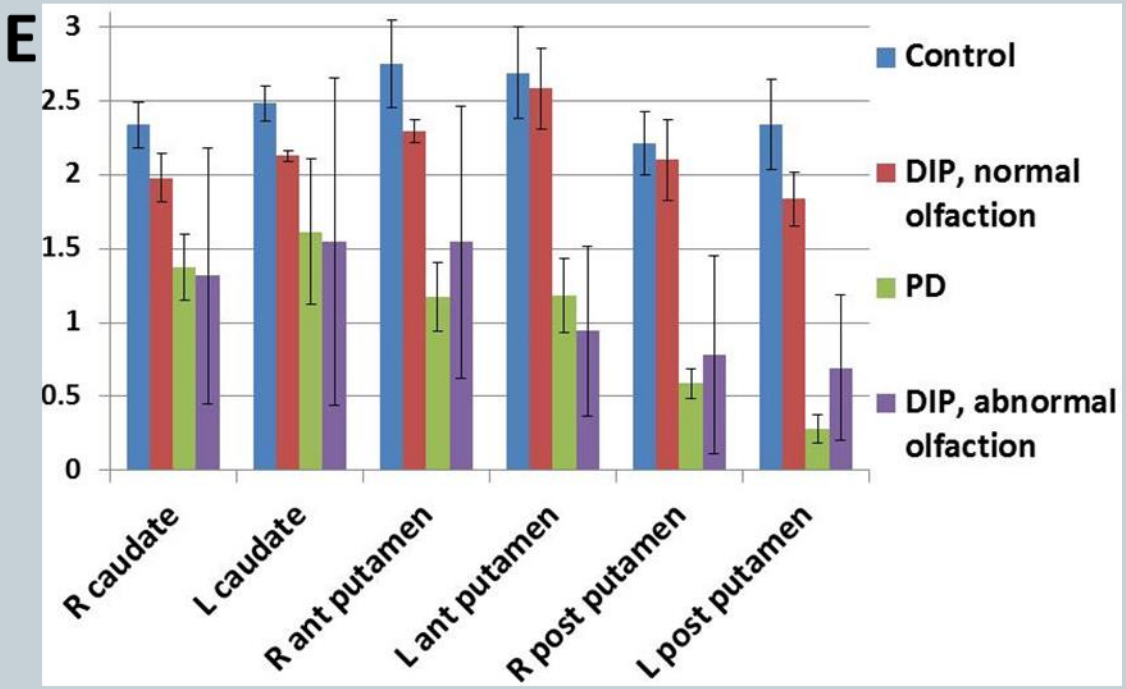
	PD vs. DIP			Persistent DIP vs. reversible DIP		
	PD N=97	DIP N=97	P	pDIP N=15	rDIP N=22	p
UPDRS-III	24 (12)	26 (15)	0.65	27 (16)	27 (16)	0.89
Tremor	3.4 (3.5)	4.4 (4.1)	0.08	4.3 (3.8)	5.9 (4.4)	0.35
Bradykinesia	10 (5.9)	9.1 (8.8)	0.32	11.3 (8.8)	7.7 (7.3)	0.16
Rigidity	5.4 (3.3)	4.9 (4.1)	0.23	5.1 (4.7)	5.9 (4.6)	0.64
PIGD	3.7 (2.3)	1.7 (1.6)	<0.001	2.2 (1.1)	0.94 (1.1)	0.003
Asymmetry index	0.29 (0.28)	0.11 (0.11)	<0.001	0.11 (0.10)	0.11 (0.15)	0.96

Non-motor symptoms in PD and DIP

	PD vs. DIP			Persistent DIP vs. reversible DIP		
	PD N=97	DIP N=97	P	pDIP N=15	rDIP N=22	p
Constipation	49%	30%	0.02	42%	20%	0.21
Lightheaded	42%	41%	1.0	50%	33%	0.34
Urinary	57%	42%	0.06	58%	40%	0.29
Impotence	47%	30%	0.05	42%	20%	0.21
Multiple autonomic	67%	50%	0.07	50%	21%	0.15
Mood	47%	61%	0.11	58%	56%	0.61
Dream enactment	51%	39%	0.15	55%	15%	0.06
Abnormal olfactory testing	88% (16/18)	28% (12/21)	0.04	86% (6/7)	16% (1/6)	0.03

Hyposmia is associated with poor recovery and dopaminergic denervation in DIP





Conclusions

- DIP is common and debilitating
- DIP occurs with both typical and atypical antipsychotics
- DIP can be impossible to distinguish from iPD
- Systematic study of management and outcomes is needed
- DIP may define a cohort at-risk for PD where non-motor symptoms including olfaction may be useful clinical biomarkers

Acknowledgements

- Drs. John Duda, Jayne Wilkinson, PADRECC clinicians
- Stephanie Pawlowski
- Adithi Kesari, Ivy Maina, Jessica Chen